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TITLE: Malignant Peripheral Nerve Sheath Tumors in Neurofibromatosis Type 1: A Multicenter Project with 3 Clinical Trials

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14. ABSTRACT

A major goal of this CTDA proposal is to optimize NF1 subject recruitment into 3 clinical trials related to MPNSTs. This CTDA project has been successful in being directly responsible for the implementation of 1 of the 3 clinical trials. Our initial efforts led to the submission of a clinical trial for neoadjuvant chemotherapy in MPNST (DAMD-NF043129; PI-David Viskochil). This proposal was not funded, however it was revised by Brigitte Widemann, M.D. as principal investigator with a dedicated focus on treatment of MPNSTs within an oncology Consortium (Sarcoma Alliance for Research through Collaboration, known as SARC). This revision entitled: PHASE II TRIAL OF NEOADJUVANT CHEMOTHERAPY IN SPORADIC AND NF1-ASSOCIATED HIGH GRADE UNRESECTABLE MPNSTs (Proposal #NF050022; PI-Brigitte Widemann) was approved for funding through the 2005 DOD NF Program. A meeting between investigators in this MPNST CTDA project and members of an MPNST Committee of a newly formed NF1 Consortium (DoD contract #W81XWH-05-1-615; PI-Jeannette Lee) and a representative of SARC was held in April, 2006, which allowed for the transition of aims from another CTDA-derived clinical trial (Identification of Risk Factors for MPNST in NF1) to potential implementation of its goals into an MPNST trial conducted through the NF1 Consortium. Finally, website development from the CTDA study is being implemented for the recruitment and the enrollment of NF1 patients with spine abnormalities into a multi-center natural history study (R01 NS050509-01A1; PI-D. Viskochil).

15. SUBJECT TERMS
MPNST – malignant peripheral nerve sheath tumor, Clinical Trial Development, NF1 – neurofibromatosis type 1; SARC – sarcoma alliance for research through collaboration

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INTRODUCTION

A major goal of this CTDA proposal is to optimize subject recruitment in each of the clinical trials. Using the prevalence estimate for NF1 as 1 in 3,500 individuals in the population at large coupled with the cross-sectional estimate of 5% affected by MPNST, we acknowledge that few centers will have more than 2 patients with MPNST and NF1 in any given year. We anticipate 1 in 1,750,000 people will develop MPNST and NF1 on an annual basis, thus the populations of the US, Canada, and Europe will provide a maximum of 50 cases per year. Our goal is to recruit at least 2/3 of this cohort for enrollment in at least 1 of the 3 clinical trials. By developing a well-publicized network of NF1 Clinic Centers and Sarcoma Centers, we plan to offer enrollment to every individual in North America and Europe who has MPNST and NF1 into the case-control trial to identify risk factors for MPNST (**clinical trial project 1**). Based on inclusion and exclusion criteria, some individuals will be eligible for the clinical trial of neoadjuvant chemotherapy, and this will be offered to them as a treatment option (**clinical trial project 3**). Subjects with symptomatic peripheral nerve sheath tumors will be offered enrollment in the PET scanning surveillance study, but this is limited to specific centers where PET scanning is available (**clinical trial project 2**). Nevertheless, those who have MPNST detected as part of clinical trial project 2 will be offered enrollment in projects 1 and 3. Finally, a portion of every MPNST that is biopsied or resected will be sent to the tumor repository at Washington University for routine analysis and storage. This core will be administered by Mark Watson, and clinicopathologic studies will be performed under the guidance of Arie Perry. Tissue samples that are processed in a standardized way may provide the most significant outcome of this multi-center proposal. Distribution of this material to other laboratories that are performing research related to NF1 and/or MPNSTs may provide further insight to their molecular pathology.

The Advisory Board and Data Analysis Committee will develop the protocols and consent forms for each clinical trial, and the Administrative Core will provide interface for each local recruitment institution via a WEB site. **A goal of this proposal is to identify and recruit a set of institutions that are capable and willing to identify and enroll subjects for each of the respective clinical trials**. This will entail an invitation to participate after protocols have been established through the respective committees, approved by the Advisory Board, and maintained on an interactive WEB site. This WEB site will be instrumental in optimizing patient recruitment and accrual, handling of image files between institutions, real-time data transfer, and collection and tracking of specimens.

KEY ACCOMPLISHMENTS

- MPNST Consortium Meeting, New York City, June, 2004
- Submission of Clinical Trial to the DoD NF Program, June, 2004 (not funded)
- Development of website through the Informatics Core of the General Clinic Research Center at the University of Utah for recruitment, enrollment, electronic protocol storage, standard operating procedures, database, and tracking.
- Submission of Clinical Trial to the DoD NF Program, February, 2005 (PI – B. Widemann, funded). Anticipated enrollment in Fall, 2006
- Funding of an NF1 Consortium Site at the University of Utah, October, 2005
- MPNST Consortium Meeting, Atlanta, April, 2006
- Submission of proposal from MPNST Committee of the NF1 Consortium to the Governing Body for inclusion in a DoD proposal for funding a clinical trial(s) in August, 2006.

BODY

Task I: Implement efficient electronic communications between all participants in the study.

Month 1 – develop server access, passwords, and orientation (oversight – Bernie LaSalle, University of Utah) for primary investigators of each project. Develop a predetermined schedule for monthly teleconferences between the primary investigators.

Months 2-6 – all relevant documents imported into WEB site at University of Utah

Months 6-9 – test reliability, data safety, confidentiality, access to dummy data on WEB site

We carried out monthly then biweekly teleconferences between in March 2004 and May 2004. Protocol documents were imported to a website and a database was developed to include entry of subjects from each of the 3 proposed projects. Bernie LaSalle supervised a team of 3 to develop a website for NF1 Centers and Sarcoma Centers to link with respect to MPNSTs. Mr. LaSalle presented this website to the primary investigators in a face-to-face meeting in New York City in early June of 2004. He was able to demonstrate access to documents, and outlined a tiered plan for different levels of data access. Sites that contributed subjects had full access to all information entered, whereas each site only had access to cumulative de-identified data from other centers. A system was established that enabled coordinators and center investigators to have restricted access to data. Project principal investigators and statisticians had access at all levels of the database.

This WEB site was not tested for reliability, data safety, or access to dummy data prior to the submission of a proposal for neoadjuvant therapy of MPNSTs. The primary focus of our WEB site was to recruit subjects for all three proposals outlined in the introduction of this report. Since our efforts were redirected specifically to a well-defined clinical trial that required treatment of MPNST, the eligibility for enrollment narrowed considerably and could be handled by the respective sarcoma centers. The focus on clinical trial project 3 de-emphasized the requirement for an extensive recruitment plan, which led to a decision to utilize a network of sarcoma centers with an organized administrative core for conduction of oncology trials. With the submission of the clinical trial our database managers simply refined the WEB site for storage, and did not activate.

Our collaboration with Bernie LaSalle and his informatics team in the Clinical Genetics Research Program of the General Clinic Research Center for the University of Utah was included in 2 grant proposals that have been successful. The first is a Department of Defense Neurofibromatosis Program award (**DAMD-NF050159**) entitled The University of Utah Clinical Genetics Research Program as an NF1 Consortium Site (PI – David Viskochil; activated 10/15/05). Our informatics team will interact with the Operations Center of the NF1 Consortium to provide data and potentially serve as unpaid consultants in the development of databases and WEB-based data management. The second grant is an NIH proposal (**R01 NS050509-01A1**) entitled Spinal Abnormalities in Neurofibromatosis Type 1. It is a multi-center, 5-year project to assess the natural history of spine problems in children with NF1 (PI – David Viskochil). Even though it is not a clinical trial, the demonstration of our collaboration with the informatics core of the University of Utah GCRC and its familiarity with NF1 translational research made this multi-center study feasible.

Dr. Widemann has also adopted a few of the protocol sheets that were part of our initial submission for her most recent proposal that has been funded through the DoD NF Program.

Task II: Complete proposals for 3 clinical trial projects.

Months 1-2 – each primary investigator finalizes their respective project goals and methods

Clinical Trial Project 1 (Jan Friedman): Identify a set of clinical, genetic and environmental risk factors that identify individuals with NF1 who are at highest risk to develop MPNSTs.

Clinical Trial Project 2 (Rosalie Ferner): Determine the value of ^{18}FDG positron emission tomography in descriminating between malignant and benign symptomatic peripheral nerve sheath tumors.

Clinical Trial Project 3 (Brigitte Widemann): Evaluate the effectiveness of neo-adjuvant therapy in MPNST treatment.

Tissue Core (Arie Perry): Develop a centralized, accessible tissue repository for PNSTs, serum, genomic DNA, RNA, cDNA, with accessible database.

Tasks: Each primary investigator will finalize their respective projects in the form of specific aims of a multi-center grant proposal. This includes: 1) specific aims with hypotheses and subaims, 2) background and significance, 3) preliminary work, 4) methods with rationale, statistical approaches, and problems and limitations, and 5) budgetary considerations.

Week 6 – Phase I meeting of the NF1-MPNST Advisory Board consisting of primary investigators and colleagues to formally present the initial drafts of the respective projects, to outline tasks for documents and procedure manuals, to define elements of a web-based database system for mutual use by personnel from each of the 5 primary sites, and nominate members of the Data Analysis Committee, the Tissue Core Advisory Committee, and the Authorship Committee.

Months 3-6 – Review and modify each clinical trial project.

Documents will be entered in the web site for review by all primary investigators and colleagues selected by each primary investigator. Each project will be finalized and integrated into a single project.

Month 6 – Phase II Meeting between primary investigators to fine-tune the budget and begin preparations for grant submission to the DOD NFRP.

Months 6-9 – Prepare final grant proposal.

Participating centers will be formally enrolled with subcontracts between respective institutions. Overall budget will be composed.

The primary investigators for each project were also involved in an NIH multicenter R01 grant submission to the NINDS for the 3 specific projects outlined above. The critiques for this proposal became available approximately 1 month after activation of this DoD Clinical Trial

Development Award. After further discussions with the DoD on the definition of a clinical trial, the 5 primary investigators decided to focus only on the project spearheaded by Dr. Brigitte Widemann (Evaluate the Effectiveness of Neoadjuvant Chemotherapy in MPNST Treatment). Our efforts culminated in the submission of a clinical trial proposal in response to the Broad Program Announcement from the NF Research Program (deadline end of June, 2004). The proposal was entitled; Phase II Trial of Neoadjuvant Chemotherapy in High-Grade, Unresectable Malignant Peripheral Nerve Sheath Tumors (**DAMD-NF043129**; PI – David Viskochil). Due to the timing of the award and need for linking with Sarcoma centers, we shifted our efforts away from the University of Utah Data Management Facility to the recruitment of a group of sarcoma centers that established themselves as a multicenter consortium of academic oncology centers (SARC – Sarcoma Alliance for Research through Collaboration) that has extensive experience in the treatment of soft tissue malignancies (sarcomas). This collaboration arose as a direct result of the MPNST Consortium Meeting held in Aspen, Colorado in May of 2002, and was extended when David Viskochil and David Gutmann presented studies on MPNST in NF1 to the Connective Tissue Oncology Society (CTOS) annual meeting held in October, 2002. Almost all member of SARC attend the annual CTOS meeting, and discussions at the meeting led to the recognition by Lee Helman, M.D. and Brigitte Widemann, M.D. as primary investigators to develop a neoadjuvant chemotherapy trial to assess the effectiveness of chemotherapy in MPSNT. These collaborations united NF1 investigators working on NF1-related MPSNTs with the SARC organization.

This proposal (**DAMD-NF043129**) was not funded. Communications between the primary investigators in reviewing the critique summary statement led to a face-to-face meeting between Jan Friedman, David Viskochil and Brigitte Widemann at the Pediatric Branch of NCI in Bethesda Maryland in January of 2005. Deliberations from this meeting led to the decision to revise the original proposal and submit with a dedicated focus on treatment of MPNST using the SARC Consortium for the bulk of the study. Brigitte Widemann was appointed the Principal Investigator, and she submitted a clinical trial award proposal to the DOD NF Research Program in February, 2005. This proposal is entitled: PHASE II TRIAL OF NEOADJUVANT CHEMOTHERAPY IN SPORADIC AND NEUROFIBROMATOSIS TYPE 1 ASSOCIATED HIGH GRADE UNRESECTABLE MALIGNANT PERIPHERAL NERVE SHEATH TUMORS (**Proposal #NF050022**), and it was funded. The study is presently under human subjects protocol review and budget negotiations. **This was a successful outcome that resulted from the collaborations directly established under the Clinical Trials Development Award.**

After full discussion, we have decided to proceed with submission of clinical trial 1 as a separate study. The goal of that trial was to identify a set of clinical, genetic and environmental risk factors that identify individuals with NF1 who are at highest risk to develop MPNSTs. Specific aims have been developed, and a draft of the objectives as developed by the co-investigators of this CTDA project is provided below:

> Individuals with neurofibromatosis type 1 (NF1) are at a relatively high risk to develop a deadly sarcoma called malignant peripheral nerve sheath tumor (MPNST) that has a 5-year survival of about 25%. Earlier detection and appropriate treatment predicts less morbidity and less mortality. Presently, it is difficult to diagnose MPNST at an early stage in disease. The identification of a cohort of individuals with NF1 who may be at high risk for MPNST would enable health care practitioners to establish rigorous screening protocols for early detection of MPSNT in NF1. **Our overall objective** as outlined in this proposal is to identify a set of clinical, genetic, molecular and environmental factors that identify those individuals with NF1 who are at highest risk to develop MPNSTs. We will use a cross-sectional case-control protocol

to determine differences between individuals with NF1 who have MPNST versus those without MPNST.

Specific aim 1: To determine if "tumor burden" is higher in those individuals with NF1 who develop MPNST, and, if so, estimate a relative risk to develop MPSNT based on "tumor load".

Specific aim 2: To identify historical factors that correlate with an altered relative risk to develop MPNST in NF1.

Specific aim 3: To identify molecular factors that correlate with an altered relative risk to develop MPNST in NF1.

As a case-control trial to identify those with NF1 who are at highest risk to develop MPNST, the defined objective and specific aims outlined herein will serve as the basis of a future proposal. Recognition that these aims could evolve from established MPNST clinical trials, including those through the NF1 consortium, led to the organization of a meeting between investigators involved in this CTDA and members of the MPNST committee of the NF1 Consortium **(DoD contract #W81XWH-05-1—615; PI – Jeannette Lee)**. The details of this meeting are highlighted in section for Task IV. The Univesity of Utah is a member of the Consortium **(DAMD NF050159)**.

With full deliberation, the investigators involved in the CTDA elected to not pursue clinical trial 2. Dr. Ferner will continue to refine the techniques and application of PET (positron emission tomography) to peripheral nerve sheath tumors in the NF1 population. She will seek independent funding through the health services research system in the United Kingdom.

Task III: Develop a WEB site for data management

Months 1-2 – Establish a core working group to modify existing database software. Primary investigators and their colleagues from each institution who will be handling data and statistical interpretation will be identified and serve on the WEB Site Development Subcommittee (WSDS). A subcommittee selected from the Data Analysis Committee with one database manager from the NNFF International Database at the University of British Columbia and one database manager from the General Clinical Research Center at the University of Utah will establish communication lines, distribute database templates, and establish draft guidelines for access and data manipulation.

Week 10 – Phase II meeting of the Data Analysis Committee to review the projects outlined by the Advisory Board, especially the statistical approaches to each respective clinical trial. This meeting will also review the outlines for documents and procedure manuals and assign tasks to develop these items to a web-based database. Members will determine design elements to be included in the NF1-MPNST WEB site.

Months 4-6 – Implement WEB site with each primary institution site.

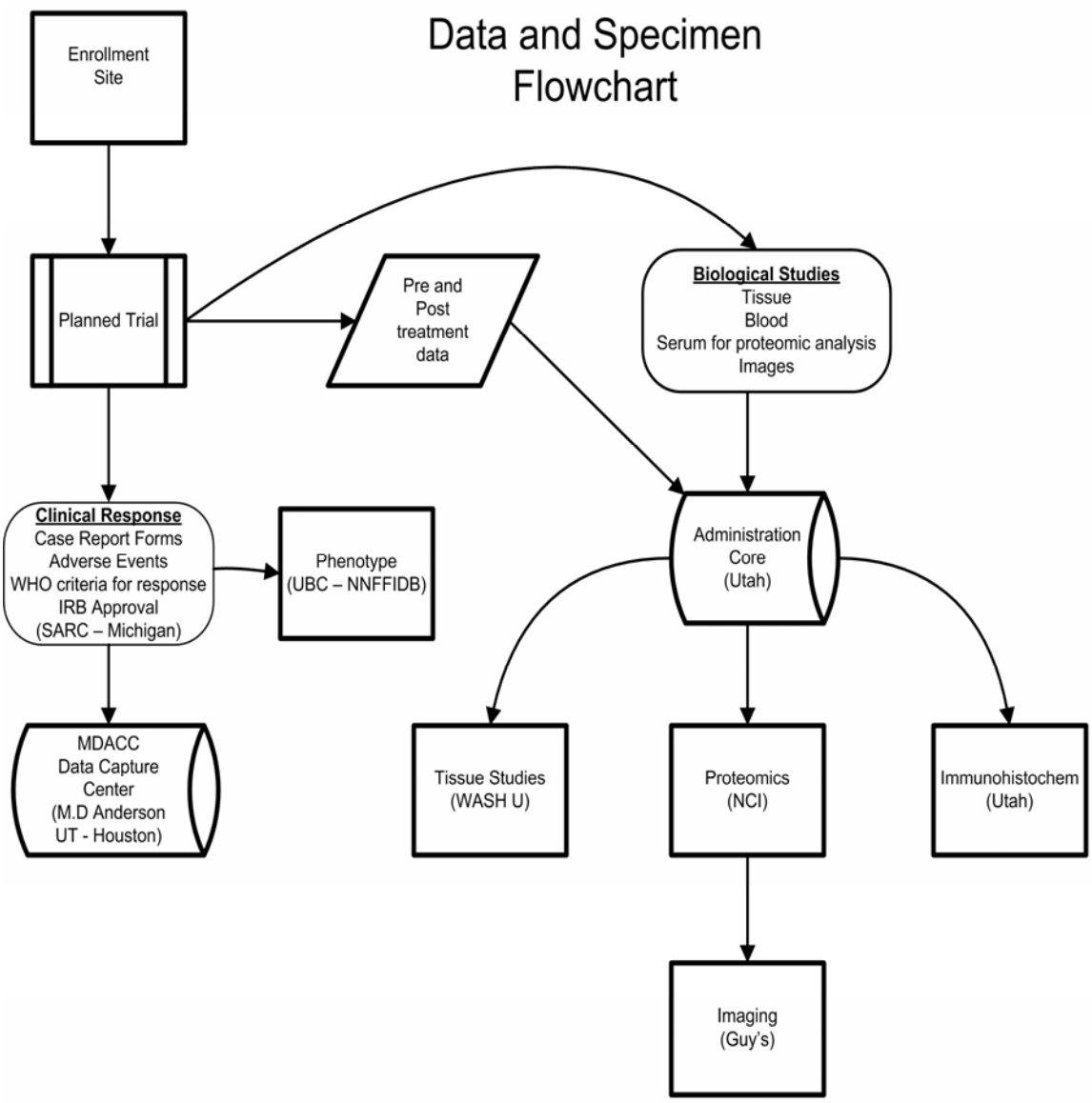
Months 6-9 – Complete troubleshooting and document the data access capabilities which will be included in the grant submission.

This task was not accomplished because of the shift in focus to use the SARC consortium to oversee all aspects of the trial including patient recruitment, data management, safety monitoring, and statistical analysis. There was no need to fully implement the WEB site developed at the University of Utah if the SARC consortium was going to collaborate with Dr. Widemann in all aspects of the clinical trial.

The Informatics Core at the University of Utah prepared to become the administrative core of the secondary aims related to MPNST biology and imaging that was part of the phase II neoadjuvant trial, however with Dr. Widemann taking over as principal investigator in the resubmission on offsite administrative core was no longer needed for this trial. The focus on this project at the exclusion of the other 2 projects also minimized the need for an administrative core to optimize recruitment and data collection. Nevertheless, the informatics core developed a website that may prove useful in deliberations within the newly formed NF1 Consortium (DoD Program Announcement for May 5, 2005 submission).

As a result of the CTDA, a website has been developed through the administrative core at the University of Utah. As designed, access to the website will include both public and restricted access. The public access provides information for both physicians and the general public regarding definitions, descriptions of ongoing studies, links to participating centers and links to the NNFF (now CTF – Childrens Tumor Foundation) and NF Inc. support group foundations. It focuses on those aspects related to MPNST. Restricted access to study data is securely provided through the use of Secure Socket Layer (SSL) technology and assigned username/password codes. The data under the SSL connection includes real time database reports regarding individual study participants. Each center is restricted to its own study population data. Summary enrollment data across all centers is also available to investigators. The restricted area contains a central document repository and up to date protocols for sample and image processing procedures. Access to the website is https://crcjs.med.utah.edu/mpnst_v2. This CTDA also funded a meeting in New York City where the website was demonstrated to participants and feedback was provided. This meeting provided Dr. Widemann with NF1-related MPNST information to present a version of her phase II neoadjuvant therapy trial at the Sarcoma Alliance for Research through Collaboration biannual meeting in June of 2004 in New Orleans. The SARC supported the trial concept, and the need to perform a clinical trial for high-grade, unresectable MPSNTs. SARC members confirmed their interest in participating in the planned trial should it be funded, and they stated that depending on the institution one could expect 1-to-4 patients at each site per year who may be eligible for the planned trial. It gave great impetus to proceed with this trial and strengthen the collaboration with SARC and CTOS. Given the success of this transition of administrative support through SARC, the MPNST WEB site at the University of Utah did not go live. However, it is presently being adapted for a multicenter trial (funded by the NINDS as R01 NS050509-01A1) for the collection of clinical data from 4 centers to determine the natural history of spine abnormalities in a cohort of 120 individuals with NF1. **As an application of WEB site development for the clinical trial for spine abnormalities in NF1, this represents a successful outcome of the CTDA even though it is not directly related to the MPNST trials.**

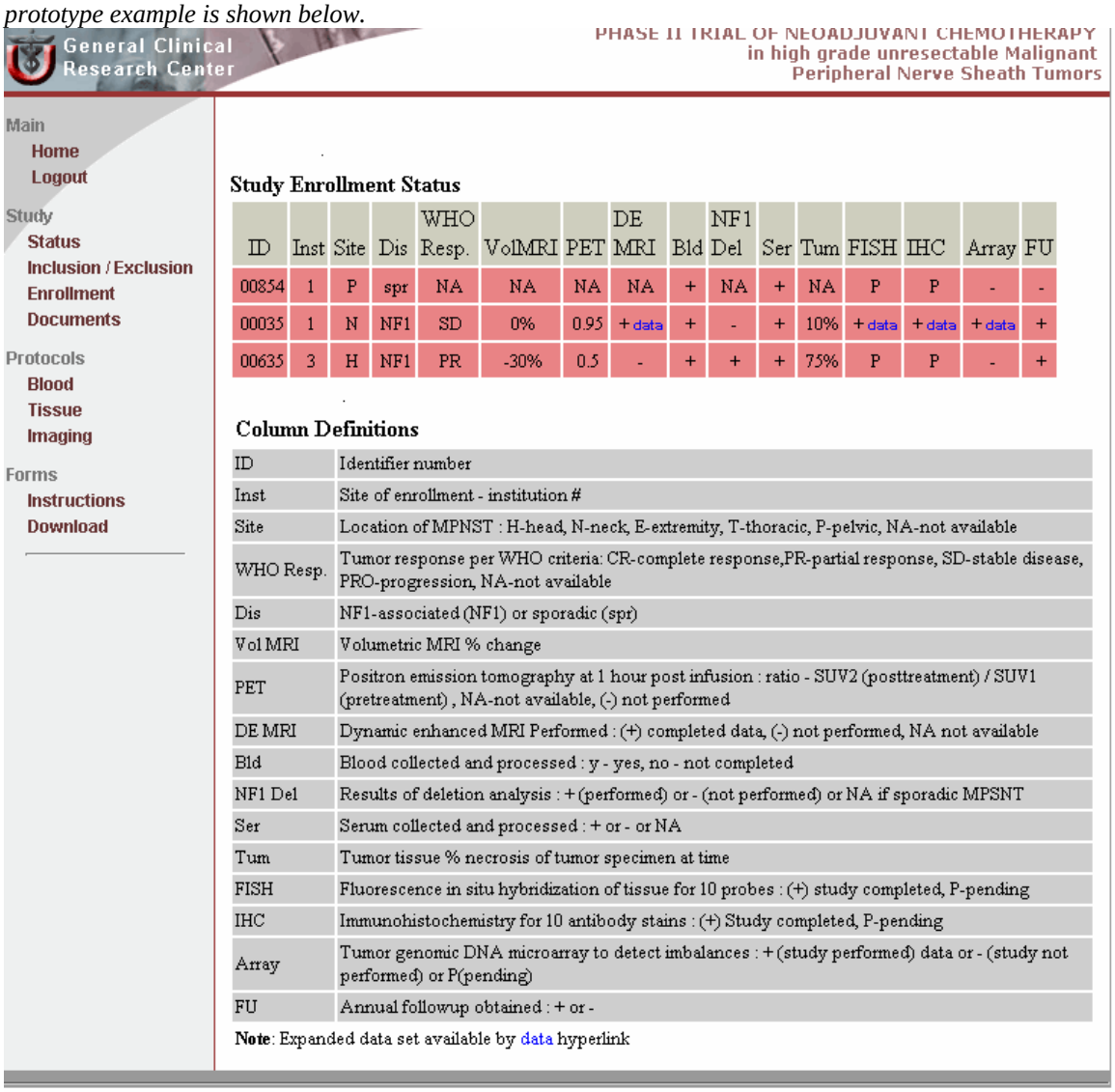
A flowchart was developed for the Clinical Trial Award submission (NF 043129) for enrollment and data and specimen collection, and it is depicted on the next page. It shows the efforts from each of the 5 centers (NCI in Bethesda, UBC in Canada, Guys Hospital in London, U of Utah (administrative core) and Washington University (tumor bank)).



In addition, a summary document showing what was available on the University of Utah Website is provided below. An interactive set up within the columns and rows was developed for querying the database. An electronic set of protocols is also embedded within the website in order for coordinators at each site to readily access protocols and fill in data collection fields within web

pages at the respective home sites. This is being modified to collect similar data for the Spinal Abnormalities Clinical Trial (PI – David Viskochil, University of Utah). Mr. LaSalle and his informatics team of the General Clinic Research Center at the University of Utah are adopting the WEB-accessible database to emphasize issues related to bone in NF1. It is anticipated to go live by the end of 2006 in order to enroll subjects from the University of British Columbia, the University of Manchester, the University of Cincinnati, and the University of Utah.

The status of data collection from the secondary objectives will be displayed through limited access website, and a prototype example is shown below.



Study Enrollment Status

ID	Inst	Site	Dis	WHO Resp.	VolMRI	PET	DE MRI	Bld	NF1 Del	Ser	Tum	FISH	IHC	Array	FU
00854	1	P	spr	NA	NA	NA	NA	+	NA	+	NA	P	P	-	-
00035	1	N	NF1	SD	0%	0.95	+ data	+	-	+	10%	+ data	+ data	+ data	+
00635	3	H	NF1	PR	-30%	0.5	-	+	+	+	75%	P	P	-	+

Column Definitions

ID	Identifier number
Inst	Site of enrollment - institution #
Site	Location of MPNST : H-head, N-neck, E-extremity, T-thoracic, P-pelvic, NA-not available
WHO Resp.	Tumor response per WHO criteria: CR-complete response,PR-partial response, SD-stable disease, PRO-progression, NA-not available
Dis	NF1-associated (NF1) or sporadic (spr)
Vol MRI	Volumetric MRI % change
PET	Positron emission tomography at 1 hour post infusion : ratio - SUV2 (posttreatment) / SUV1 (pretreatment) , NA-not available, (-) not performed
DE MRI	Dynamic enhanced MRI Performed : (+) completed data, (-) not performed, NA not available
Bld	Blood collected and processed : y - yes, no - not completed
NF1 Del	Results of deletion analysis : + (performed) or - (not performed) or NA if sporadic MPSNT
Ser	Serum collected and processed : + or - or NA
Tum	Tumor tissue % necrosis of tumor specimen at time
FISH	Fluorescence in situ hybridization of tissue for 10 probes : (+) study completed, P-pending
IHC	Immunohistochemistry for 10 antibody stains : (+) Study completed, P-pending
Array	Tumor genomic DNA microarray to detect imbalances : + (study performed) data or - (study not performed) or P(pending)
FU	Annual followup obtained : + or -

Note: Expanded data set available by data hyperlink

THIS IS AN EXAMPLE ONLY. DOES NOT REFLECT ACTUAL ENROLLMENT

Task IV: Recruit Sarcoma Centers and NF Centers for participation in each project.

Month 3 – Identify potential participating centers for each of the 3 projects.

Months 4-8 – Establish agreements with participating centers and document these agreements in the form of support letters.

Month 9 – Assimilate all support agreements in the grant submission.

This was a partially successful outcome. By shifting the focus of this clinical trial development award to chemotherapeutic intervention in MPNSTs rather than natural history trials attempting to identify predisposing factors leading to MPNST in the NF1 population, we de-emphasized the development of NF1 centers and established an MPNST trial within an existing Sarcoma Consortium. The SARC centers were identified, and are now aware of the important association of MPSNTs and NF1.

There are a number Sarcoma Centers affiliated with academic institutions scattered throughout North America and Europe. Oncologists who specialize in sarcoma care have also organized themselves into a vibrant working group called the Connective Tissue Oncology Society (CTOS). In 2001, a number of members with common interest in sarcoma trials formed the North American Sarcoma Study Group of the CTOS to collaborate on clinical trial efforts. This loose-knit consortium opened its first trial in November, 2001 and a second one in January of 2003. By November of 2003, a formal structure was established with the application and incorporation of SARC (Sarcoma Alliance for Research through Collaboration) as a not-for-profit organization. SARC acts as an advocate for sarcoma medical research. Its primary role is to advocate for the conduct of clinical trials relating to treatments for sarcoma. SARC facilitates dialogue and collaboration among sarcoma researchers and clinicians, assists in the development and dissemination of protocols for clinical trials and information relating to sarcoma research and the results of clinical trials, administers research grants and funding for clinical trials, and acts as a primary resource for those treating sarcoma. Members of SARC include sarcoma experts from the following centers listed in APPENDIX 1. Membership requirements include multidisciplinary membership to the Connective Tissue Oncology Society and a commitment to sarcoma research.

As one of the rare sarcomas, MPNST is not a “high-profile” tumor. Therefore, we have elected to work with the SARC as the operations center to implement this phase II clinical trial. Unlike pediatric cancer trials developed through the Childrens Oncology Group, well-established clinical trials using protocols to treat MPNSTs in a consistent manner throughout the oncology community have not been widely instituted. In reviewing the oncology literature, there are approximately 10 clinical trials available for MPNSTs (clinicaltrials.gov web page), and 44 trials for unspecified soft tissue sarcomas. The support and involvement of SARC provides an infrastructure to maximize enrollment of these rare patients.

The DoD award to Dr. Widemann (**NF050022**) will ensure the establishment of participating centers that will also likely participate in future studies that include natural history studies of MPSNTs and NF1. David Viskochil has attended the last 3 meetings of the connective tissue oncology society meeting and he has presented posters at each. This annual meeting includes all the SARC consortium centers, and Dr. Viskochil will attend a SARC biannual meeting as a satellite meeting of the CTOS meeting in Boca Raton, Florida on November 17, 2005. The next meeting is scheduled November 2-4, 2006, and Dr. Viskochil will present a poster on loss of heterozygosity of the *NF1* gene in tibial pseudarthrosis tissue derived from individuals with NF1. There are no other geneticists at this meeting, and his presence will enable the sarcoma center personnel to continue to

recognize the association of NF1 with MPNST. An associate of Dr. Widemann will present the protocol of the DAMD proposal to SARC representatives. There are only 6 sarcoma treatment trials that are presently administered by the SARC consortium, and this protocol would be one of the trials. Dr. Widemann has recruited the following centers for her Phase II study:

Selected neurofibromatosis type 1 and pediatric sarcoma referral centers:
Steward Goldman, MD, Children's Memorial Hospital, Chicago, IL
Regina Jakacki, MD, Children's Hospital of Pittsburgh, Pittsburgh, PA
Nita Seibel, MD, Children's National Medical Center, Washington, DC
Jean Belasco, MD, Children's Hospital of Philadelphia, Philadelphia, PA
Robert Arceci, MD, Johns Hopkins Oncology Center, Baltimore, MD
Alyssa Reddy, MD, University of Alabama at Birmingham, AL
John Perentesis, MD, Cincinnati Children's Hospital, Cincinnati, OH
Allison King, MD, St. Louis Children's Hospital, St. Louis, MO
Christopher Moertel, MD, Children's Hospitals and Clinics of MN, St.Paul, MN

In addition to the identification of participating sarcoma centers for Dr. Widemann's clinical trial, investigators of the CTDA met with MPNST committee members of the newly established NF1 consortium **(DoD contract #W81XWH-05-1-615; PI – Jeannette Lee)**. The NF1 Consortium is comprised of 9 sites in the United States and an Operations Center. Its objectives are 1) to accelerate the clinical translation of basic NF1 research and ultimately decrease the overall impact of the disease, and 2) Conceive, develop, and conduct collaborative pilot, phase I and II clinical evaluations of promising therapeutic agents or approaches for the management or treatment of NF1. The 9 sites are academic centers from Birmingham, Boston, Washington DC, Cincinnati, Bethesda, Chicago, St. Louis, and Utah. The meeting between the MPNST Consortium of the CTDA and the MPSNT committee of the NF1 Consortium was organized by Dr. Viskochil to transition the goals of 1 of the CTDA-developed studies (identify risk factors for the development of MPNST in NF1) to implementation by incorporation into clinical trials for MPNST developed through the NF1 Consortium. The meeting was held on April 6, 2006 in conjunction with the NF1 Consortium Meeting that was held on April 7, 2006 in Atlanta. In addition to members of the MPNST Committee of the NF1 Consortium and members of the MPNST Consortium from the CTDA, Dr. Larry Baker from SARC joined us to review progress by CTDA investigators and inform the attendees about the infrastructure of SARC. Attendees to this meeting are bolded in the list on the next page

MPNST Committee of the NF1 Consortium

Chairs:
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MPNST Consortium from the Clinical Trials Development Award (DoD)

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David Viskochil, Univeristy of Utah
Brigitte Widemann, NCI, Pediatric Branch

Ad hoc Invitees

Laurence Baker, University of Michigan (SARC)
Karen Cichowski, Harvard University
Shyra Miller, University of Cincinnati

Dr. Jeannette Lee is the PI for the NF1 Consortium Operations Center. She oversaw the submission of the Clinical Trials Proposal that was submitted in August, 2006 in response to a Program Announcement by the DoD NF Program. The chairs for the MPNST Committee of the NF1 Consortium are Drs. John Perentesis and Karen Albritton. Drs. Karen Chichowski and Shyra Miller are ad hoc attendees who gave presentations to the group. The agenda for the meeting is provided below:

AGENDA

0930 Introductions; past history of MPNST consortium - D Viskochil
1000 Summary of MPSNT protocol(s) for the NF1 Consortium - J Perentesis
1030 Epidemiology of MPNST in NF1 - J Friedman
1100 Diagnostic Imaging of MPNST and Plexiform neurofibromas - R Ferner
1130 Clinical Trial of Neoadjuvant Therapy in NF1 - B Widemann
1200 SARC - L Baker
1230 Lunch
1300 Ras-neurofibromin Signal Transduction Pathway - K Cichowski
1330 Gene Expression Patterns in Peripheral Nerve Sheath Tumors – S Miller
1400 Immunohistochemical Patterns in PNSTs – D Viskochil
1430 Break
1500 Open Discussion on Potential Protocols

Anticipated Meeting Outcomes

Identify potential biologic agents for future clinical trials
Specify primary and secondary endpoints for MPNST treatment protocols
Identify limitations of NF1 Consortium and Operations Center in MPNST Trials
List collaborative agencies that could facilitate NF1 MPNST Trials
Identify mechanisms to enroll MPNST and control subjects into longitudinal registries

At the conclusion of the meeting the attendees had addressed the above agenda items. A major outcome was the identification of 2 unique signaling pathway targets for MPNST treatment protocols, Erk in the mitogen activated protein kinase pathway and mTOR. The endpoints for treatment protocols were accepted as survival and tumor response by volume loss. Limitations of multicenter trials were described, and attendees acknowledged the value of consortia to enroll and complete data acquisition with due respect for safety monitoring. Presently, the 2 collaborative agencies that are prepared to facilitate NF1 MPNST trials were identified as the NF1 consortium and SARC. Mechanisms to enroll patients and controls for longitudinal registries were viewed as intimately tied to the roll-out of protocols for treatment of NF1-associated MPNSTs.

Over the course of the ensuing months Drs. Brian Weiss and Brigitte Widemann worked closely with the chairs to develop a clinical trial for MPNST that was included in the DoD proposal submitted by Dr. Lee for 4 clinical trials. The MPNST trial was embedded in section 8 of the proposal, and the primary hypothesis which evolved in part from the April meeting states: Targeted inhibition of signaling pathways upstream and downstream of the ras/NF1 pathway (e.g. Raf, P13K, RalGEF) will effectively and selectively inhibit the growth and progression of NF1-related MPNST. The primary specific aim to address this hypothesis is: To determine if combination multikinase inhibitors and chemotherapy will be effective in treating children with NF1 and relapsed MPNST. This protocol is tied to those individuals who have entered and not responded to Dr. Widemann's protocol (PHASE II TRIAL OF NEOADJUVANT CHEMOTHERAPY IN SPORADIC AND NEUROFIBROMATOSIS TYPE 1 ASSOCIATED HIGH GRADE UNRESECTABLE MPNSTs), and demonstrates the value of linking the SARC infrastructure with the NF1 Consortium.

CONCLUSION

This project has been successful in being directly responsible for the implementation of a clinical trial for MPNSTs in NF1 patients (project 3). It has not led to the successful implementation of clinical studies outlined in projects 1 and 2. We have elected to drop ongoing pursuit of funding for the studies outlined in project 2. This decision was predicated on discussions between radiologists familiar with PET scanning in sarcoma centers, which took place in the face-to-face meeting in New York City and teleconference calls as part of the planning for the neoadjuvant chemotherapy clinical trial. The PET protocols outlined by Dr. Ferner in project 2 may not be enthusiastically implemented in the United States. The studies outlined in project 1 to identify individuals with NF1 at higher risk to develop MPNST have been refined and will be submitted for funding review in the future. A final face-to-face meeting of the MPNST Consortium of the CTDA was held with the MPNST Committee of a newly formed NF1 Consortium and a representative from the Sarcoma Alliance for Research through Collaboration (SARC) to transition deliberations and protocol design for this clinical trial to implementation with active trials.

APPENDIX 1 – PARTICIPATING SITES INFORMATION

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